REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-51 and 69-73 were pending for purposes of this Office Action, as claims 52-68 were previously canceled in response to a Restriction Requirement.

Claims 18-23, 25-29, 39-46, 71 and 73 were previously canceled by the amendment dated June 11, 2008.

Claims 1-17, 24, 30-38, 47-51, and 69-70 and 72 remain pending.

Reconsideration is respectfully requested.

II. Double Patenting

The rejection of the claims 1-17, 24, 30-38, 47-51, 69-70, and 72 on the ground of nonstatutory obviousness-type double patenting over co-pending U.S. Application No. 10/413,022 in view of U.S. Patent No. 5,476,093 has been maintained.

Applicants respectfully submit that consideration will be given to the filing of a terminal disclaimer upon notification that the pending claims are otherwise allowable.

III. Claim Rejections- 35 U.S.C. § 103

In the current Office Action, claims 1-17, 24, 30-38, 47-51, 69-70 and 72 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. 2002/0006933 to Gupta et al. ("the Gupta publication") in view of U.S. Patent No. 5,699,789 to Hendricks ("the Hendricks patent"); Ensuring Patient Care, 2nd ed., 1999, pages 15-21; U.S. Patent No. 5,476,093 to Lankinen ("the Lankinen patent"); and Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647).

Applicants respectfully traverse the rejection and submit that the combination of references cited in the Office Action does not teach or suggest the present invention as claimed. The claims of the present invention are directed to a method for treating sexual dysfunction in a human via inhalation of a powder composition comprising a low dose of apomorphine (100-1600 μg), which is sufficient to provide a therapeutic effect in less than about nine minutes following inhalation, wherein the method is not associated with adverse side effects normally associated with administration of apomorphine.

The Gupta publication, US 2002/0006933, is concerned with treating sexual dysfunction using apomorphine. As admitted in the Office Action, the Gupta reference "does not expressly teach the dose of apomorhine" as recited in the present invention. See Office Action, page 5, line 16. Moreover, the Gupta publication, as shown in Example 2, discloses the administration of apomorphine by instillation (i.e., using a solution), as a *model* of inhalation. Applicant's following submissions substantiate the point that instillation is an unsuitable model of inhalation. Thus, certain limitations are inherent in the teaching provided by the Gupta publication, and would not have made obvious the specific invention as now claimed in the subject application. Gupta does not disclose inhalation in any form, but only instillation as a model of inhalation. Instillation is the use of a solution to deliver a drug, to represent administration of an aerosolized drug. Applicants attach herewith as Appendix A, a paper entitled "Pulmonary Distribution of Particles Given by Intratracheal Instillation or by Aerosol Inhalation" which discloses that the distribution pattern of intratracheally instilled particles differs considerably from that produced following inhalation of comparable particles. See Brain *et al.,* "Pulmonary Distribution of Particles Given by Intratracheal Instillation or by Aerosol Inhalation" Environmental Research, volume 11, pages 13-33, 1976. Pathological studies demonstrate that instillation results in heavy more centralized deposits, whereas the inhalation pattern is lighter and both, more evenly and more widely distributed. See Brain *et al.,* "Pulmonary Distribution of Particles Given by Intratracheal Instillation or by Aerosol Inhalation," Environmental Research, volume 11, conclusion section. Accordingly, it is not possible to draw conclusions regarding the inevitable effects of inhalation of a component from an instillation experiment of the same component.

Moreover, the Examiner's attention is directed to paragraph [0074] of the Gupta publication, where it is stated that "[a]n 8 mg human dose compares well with about 1.33 mg apomorphine dose in dogs." Applicants submit that the inhaled dose range described in the Gupta publication US2002/0006933 is equivalent to a 3-12 mg human dose range – well above the 0.1-1.6 mg dose as claimed for the subject invention. To reiterate, as admitted in the Office Action, the Gupta reference "does not expressly teach the dose of apomorhine" as recited in the present invention. See Office Action, page 5, line 16.

In addition, Applicants re-assert that while pharmacokinetic parameters were presented in Example 2 of the Gupta publication, there were no pharmacodynamic data presented or even commented upon. Accordingly, there is nothing in the Gupta publication (which describes only the use of apomorphine solution, and only speculates that powder compositions can be used) that teaches or suggests that inhalation of apomorphine powder, at the doses tested, could achieve a therapeutic effect.

Certainly, the Gupta publication does not describe using a powder composition that can achieve a therapeutic effect within less than about nine minutes, as claimed in the present invention. As shown in Table 4 of the Gupta publication, the doses of apomorphine administered by "inhalation" (using instillation as a model) led to a C_{max} being achieved after 0.17 h, which is more than 10 minutes after administration. The subject application now claims "a therapeutic effect in less than about nine minutes." The rapid uptake of apomorphine into the blood following inhalation of the powdered formulations of the invention means that C_{max} is reached quickly. Thus, applicants believe the Gupta publication does not meet the limitations of low dose, rapid effect, and lack of associated side effects as recited for the claimed invention. Moreover, applicants believe there is no teaching or suggestion in US2002/0006933 that would lead a person of ordinary skill in the art to modify what is described in the Gupta publication and thereby arrive at the claimed dose, time to therapeutic effect, and lack of associated side effects, as claimed.

A further feature recited in claim 1 of the present invention is that inhalation of the dry powder composition comprising low-dose apomorphine is not associated with the adverse side

effects normally associated with the administration of apomorphine. The rapid C_{max} which is reached by the subject invention, coupled with the short half-life that is associated with inhaled apomorphine, minimizes the period in which any side effects will occur. Data from the study described in Example 14 of the present application consequently show the powdered apomorphine inhaled by the patients to be essentially free of associated adverse effects.

This advantage provided by the subject invention is a vast improvement over the 'instillation/inhalation' of apomorphine reported in the Gupta publication, where nearly every subject in the study suffered emesis within the first five minutes after inhaling the drug (see Table 3). This adverse side effect occurred using the method described in the Gupta reference despite the fact that the study was clearly designed to show apomorphine administration did NOT produce this adverse side effect.

The Office Action asserts that the Gupta reference ('933 reference) also teaches 0.25-5 ng/ml plasma concentration of apomorphine "with much less side effects such as emesis and at the same time being useful in treating sexual dysfunction (See paragraph [0023] and [0073])." See Office Action, page 5, lines 8-10. However, Applicants respectfully submit that Paragraph 74 of Gupta indicates that studies were carried out to achieve plasma drug levels in dogs comparable to or higher than those achieved with 2 milligrams sublingual tablets in dogs without comparable side effect. 2 milligrams apomorphine in dogs delivered in a sublingual manner gives a C_{max} of 7.75 and an emesis incidence of 50%, with one dog responding at 15 minutes and one at 30 minutes. In contrast, in Table 3 of Gupta, it is seen that the so called instillation/inhalation route gives either 80% or 100% emesis at 0 or 5 minutes. Clearly, therefore, the aim of Gupta to achieve plasma drug levels *without comparable side effects* has not been achieved.

To further illustrate this point, it is noted that the Gupta publication shows the inhalation route of administration, itself, is a contributory factor in the incidence of emesis observed. For example, the inhalation of a dose of 1 mg apomorphine led to a C_{max} of 31.5 ng/ml (Table 4). The administration of 20 mg apomorphine by oral gavage led to a very similar C_{max} of 29.3 ng/ml (Table 6). All five dogs in the instillation/inhalation study suffered immediate emesis

upon inhaling the dose of apomorphine (Table 3). In contrast, only two out of five dogs suffered immediate emesis following the oral dose of apomorphine (Table 5).

Thus, although paragraph [0035] of the Gupta publication (US 2002/0006933) suggests that apomorphine may be administered as a dry powder by inhalation, the skilled person clearly would not have been motivated to do this, on the logical assumption that it would invariably be accompanied by immediate emesis. Moreover, when considering Gupta as a whole, other routes of delivery given in Gupta appear to be preferable to instillation. Applicants remind the Examiner that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. See W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). For example, in Table 2 of the Gupta reference, intranasal delivery of apomorphine gives a C_{max} in the range of 139 and 1,152 ng per ml. This is much higher than via the instillation route given in Table 4, where C_{max} ranges from 15 to 65. The skilled person would, therefore, consider intranasal administration to be more preferable route of administration for apomorphine than instillation. As shown in Table 3 of Gupta, the incidence of emesis in dogs is 100% for the instillation model for apomorphine administration. In comparison, the emesis effect is far less severe for other delivery routes, such as intranasal or oral delivery. Accordingly, given the teaching of Gupta, a skilled person would prefer other approaches, such as intranasal or oral delivery over instillation/inhalation. The skilled person certainly would not have expected the benefits that are associated with the inhalation of powder formulations of the present invention, namely the rapid onset of a therapeutic effect, using a relatively low dose, yet without induction of the adverse side effects normally associated with the administration of apomorphine.

None of the other cited references (U.S. Patent No. 5,699,789 to Hendricks; Ensuring Patient Care, 2nd ed., 1999, pages 15-21; U.S. Patent No. 5,476,093 to Lankinen; Lucas et al., (Pharmaceutical Research, 1999; 16(10):1643-1647) cure these defects of the Gupta publication. Specifically, these other cited references fail to teach the administration by inhalation of a dry powder composition at a dose of between about 100 to about 1600 μg of apomorphine. In fact, while these other references are concerned with inhalation therapy, and are cited for describing

similar particle size ranges or propellants used for an inhalation composition, none of them relate to apomorphine or treatments for sexual dysfunction and thus cannot be readily adapted to, or readily applied to modify, the teaching of the Gupta publication in order to cure the defects of the primary reference.

Neither do these other cited references describe that such administration provides a therapeutic effect in less than about nine minutes without inducing the adverse side effects normally associated with the administration of apomorphine. A person skilled in the art concerned with the administration of apomorphine for the treatment of sexual dysfunction would therefore not find in these other cited references any teaching or suggestion regarding the relatively low dose and relatively rapid onset of therapeutic effect provided by the subject invention, which are claimed in the subject application, but are clearly missing from the Gupta publication.

The fact that inhalation of a dry powder comprising a low dose of apomorphine provides a therapeutic effect in less than about nine minutes, but is not associated with the adverse side effects normally associated with the administration of apomorphine, would not have been obvious from the Gupta publication, taken alone, or in combination with the other cited references. The skilled person would not have been motivated to substitute a dry powder composition for the solutions described in Example 2 of the Gupta publication and would not, therefore, have arrived at the methods as recited in the amended claims.

Lastly, in response to the Examiner's statement on page 6, lines 16 to 18 of the Office Action that "the optimization of dosage range herein claimed in order to achieve the optimal therapeutic plasma level of apomorphine is obvious as being within the skill of the artisan," Applicants note that "obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that result in the claimed composition." *Appeal No. 2007-4423, Decision of Appeal dated July 23, 2008.*

For the foregoing reasons, Applicants submit that the combination of the cited documents does not render the present claims obvious, and respectfully request withdrawal of the obviousness rejection under 35 U.S.C. § 103(a).

CONCLUSION

Reconsideration of the present application, as amended, is requested. The Examiner is respectfully requested to telephone Applicant's undersigned attorney in order to resolve any outstanding issues and advance the prosecution of the case to allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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